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THE DECONDITIONING EFFECT OF SOME β-AMINOKETONES, A NEW GROUP OF TRANQUILIZERS

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In an earlier paper[1] we reported the development of a method for the quantitative assessment of the deconditioning effect of tranquilizers.

Fig. 1 shows the experimental arrangement. The unconditioned stimulus (US) is a shock administered by the grid. Experiencing the shock, the rat jumps to the top of the glass cylinder. A conditioned response quickly develops. Using an alternating current of 1.0 V as US a conditioned response is built up which cannot be inhibited by the so-called minor tranquilizers, *e.g.* meprobamate. It is also resistant to the classical sedato-hypnotic drugs, for example barbiturates, but it is possible to demonstrate the deconditioning effect of even small doses of major tranquilizers. We could demonstrate by this jumping-test that 0.5 mg/kg reserpine, 1 mg/kg of the reserpine-like substance tetrabenazine, and 3 mg/kg of chlorpromazine are equally potent in their deconditioning effect.

In further experiments we have sought new compounds which would exert a deconditioning effect in this test. We found that a β-aminoketone, 2-piperidinomethyl-tetralone · HCl (NA 86), synthesized by MANNICH in 1922[2], possesses such an effect[3]. Starting from this substance we synthesized new β-aminoketones, examining the relationship between tranquilizing effect and structure.

Table I contains only a few of the characteristic molecules chosen from the 19 new compounds so far synthesized. The first, NA 86, is the one synthesized earlier by MANNICH. As we have shown in our previous work[3] it possesses both tranquilizing and anticonvulsant action.

Table I shows the structure of the molecules and the characteristic pharmacological data of the compounds. The ED_{50} value of toxicity, motility-inhibiting, deconditioning and anticonvulsant action, as well as the ED_{100} value of narcosis-potentiating effect are given. Relative activities are also calculated. The action of NA 86 is taken as unit.

Our experiments showed that changing the methylpiperidine-group of NA 86 leads to a diminution of all effects investigated. This phenomenon is demonstrated in the Table by the compound N 671, the morpholine derivative of NA 86. This compound is less toxic than the starting molecule. The deconditioning and anticonvulsant effects show a very marked decrease and the motility-inhibiting effect is also diminished, although certainly not to the same degree. On the other hand, the narcosis-potentiating effect, although somewhat weaker than in NA 86, remains relatively unaffected.

Substitution at position 4 increases the toxicity and a parallel increase in the anticonvulsant effect of the molecule is also apparent. Compound N 642 shows the

ENCLOSURE "A"

effect of the substitution of a methyl group at position 4. It is evident from the Table that this position is toxophorous. The rise in toxicity is paralleled by an increase in the anticonvulsant effect. The narcosis-potentiating effect of the molecule remains unchanged, but the tranquilizing effect is somewhat weaker than that of NA 80.

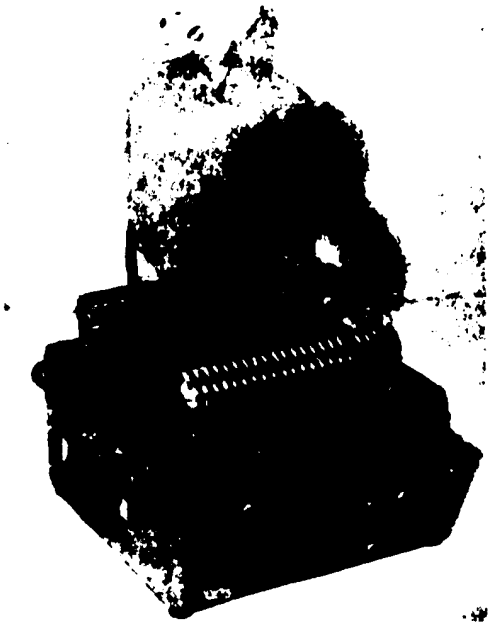


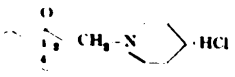
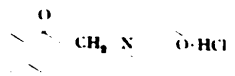
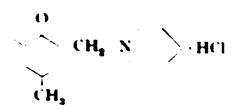
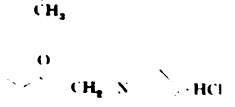
Fig. 1. Arrangement for building up a conditioned response in rats.

Substitution at positions 6 and 7 have an opposite effect. As seen from the Table, compound N 702, the 6,7-dimethyl-derivative of NA 80 shows a much lower toxicity than the starting molecule. Narcosis-potentiating and also anticonvulsant effects decrease, but the tranquilizing effect greatly increases. The deconditioning action and hypermotility-inhibiting action of the drug also increase. In the case of the new β-aminoketones there is no correlation between narcosis-potentiating capacity and tranquilizing effect.

Among the 19 new compounds so far synthesized, N 702 possesses the strongest tranquilizing effect. There is but slight difference both in deconditioning and amphetamine-hypermotility inhibiting effect between N 702 and chlorpromazine. N 702 also inhibits hypermotility of mice caused by phenmetrazine, morphine or cocaine. However, its antiamphetamine effect is relatively the strongest.

The motility of mice and rats was measured with the aid of a new apparatus operating on the following principle. Metal plates are fastened side by side, 3 mm apart. They are connected in such a way that if a mouse or a rat passes over two neighbouring plates, a circuit is closed and in consequence the pattern of movement is electronically measured. Motility count is a number representing the average number of circuits

TABLE I

Compound	Toxicity (mice) LD^{50} mg/kg	Toxicity (mice) Relative activity	Narcosis-potentiation (rats) ED^{50} mg/kg	Narcosis-potentiation (rats) Rel. at.	Motility inhibition (mice) ED^{50} mg/kg	Motility inhibition (mice) Rel. act.	Deconditioning effect (rats) ED^{50} mg/kg	Deconditioning effect (rats) Rel. a.t	Anticonvulsant effect (rats) ED^{50} mg/kg	Anticonvulsant effect (rats) Rel. a.t.
NA 86 	135	1.00	50	1.00	5.6	1.00	4.8	1.00	8.25	1.00
N 671 	330	0.40	70	1.00	12.1	0.46	34.3	1.00	70.5	0.11
N 642 	62	2.16	50	1.00	6.7	0.84	7.1	0.67	3.9	2.11
N 702 	250	0.62	80	0.62	0.66	8.48	1.6	3.00	54.5	0.15
Chloropromazine					0.65	8.61	1.3	3.69		

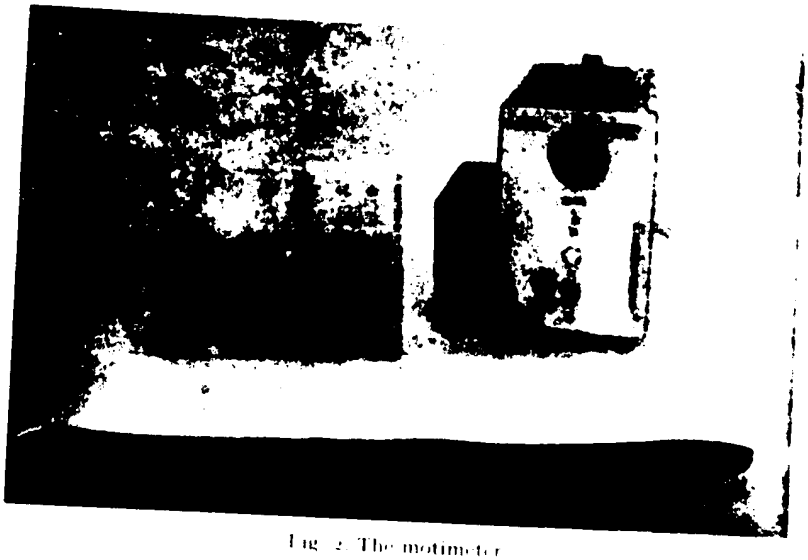


Fig. 2. The motimeter

closed in one hour. The intensity of the current flowing through the body of an animal passing over two neighbouring metal plates is not more than 5 μA, it therefore has no biological effect.

Fig. 2 shows a small two channel device for experiments with mice. We also devised a large instrument which allows the simultaneous measurement of the motility of 24 mice one by one, or of one rat.

Fig. 3 shows the psychostimulant effect of amphetamine measured with the motimeter. Motility count is plotted against the dose of the psychostimulant and as seen from the figure, a linear relationship exists between dose and effect. The curve declines

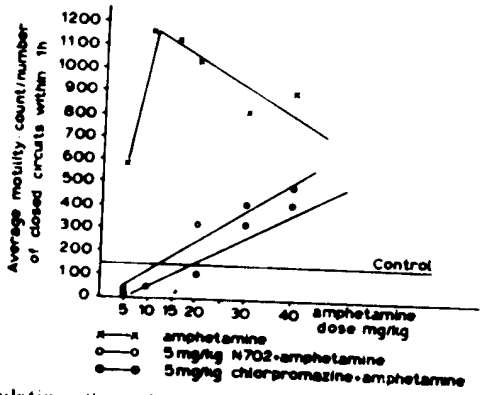


Fig. 3. Stimulating effect of aruphetamine measured with the motimeter

when large doses of amphetamine are given. The second dose response curve shows the action of the same doses of amphetamine if given together with 5 mg kg of N 702. The third curve shows the effect of 5 mg kg chlorpromazine. The curves clearly indicate

that both drugs inhibit the hypermotility caused even by high doses of amphetamine. The action of N 702 hardly differs from that of chlorpromazine.

The results demonstrate that some β-aminoketones behave as major tranquilizers in experiments on mice and rats. The pharmacological effect of further modifications of the starting molecule is under investigation.

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3 J. KNOLL, *Arch. exptl. Pathol. Pharmakol. Naunyn Schmiedebergs*, 92 (1959) 92; 238 (1960) 114.

Arch. int. pharmacodyn., 1961, No 1-2.

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MOTIMETER, A NEW SENSITIVE APPARATUS FOR THE QUANTITATIVE MEASUREMENT OF HYPERMOTILITY CAUSED BY PSYCHOSTIMULANTS

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In both pharmacology and physiology it is often desirable to obtain reliable quantitative data as to the motility of animals, most often of very agile rodents (mice, rats), which are best suited for use in such studies.

In motility experiments either the "total motility" is measured, or a "pattern of movement" is selected and the frequency with which it occurs is recorded.

Until now, it was only the photocell method of WINTER and FLATAKER (1), as modified by DEWS (2) that employed the "pattern of movement" procedure. The advantage of the device measuring the frequency of a pattern of movement is that only such compounds give a significant rise in motility which exhibit an increase of coordinated motor activities (running, walking, searching, orientation, etc.), while drugs producing incoordination, convulsions or fibrillation are without effect.

The photocell aparatus has the disadvantage that measurement is unreliable when the animal stops in front of the photocell, blocking the way of the light. Therefore the animals must be kept under surveillance throughout the experiment. Moreover, in studies concerned with coordinated motor activities involving large areas, such as "hunger motility", "object finding", etc. (3. 4. 5) the photocell arrangement is absolutely uneconomical and much too complicated.

We have therefore developed an extremely sensitive electronic apparatus called the "motimeter", which measures a "pattern of movement", is suitable for use in both pharmacological and physiological

ENCLOSURE "B"

studies and may be applied to large numbers of animals at the same time and measures their motility completely automatically.

Description of the instrument. Principle of operation of the motimeter. As shown in FIG. 1 the animal moves over four aluminium plates 12 × 9,5 cm and the counter counts every passage between two plates. The plates are spaced at 3 mm. A beam tetrode 6AQ5 with grid control is used for counting. The auxiliary grid is short-circuited with the anode. The negative bias voltage of the grid is led through a resistance of 10 MΩ upon the effect of which the tube blocks, i.e. it does not conduct.

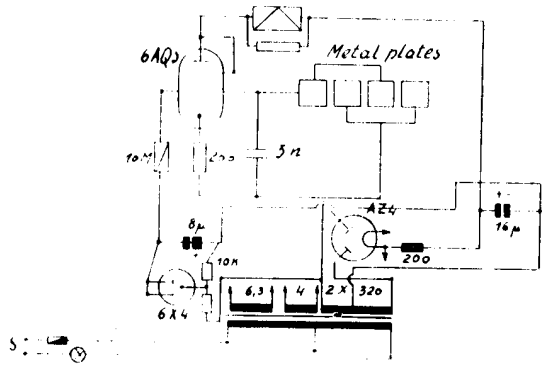


FIG. 1

Under our experimental conditions a current of an intensity not exceeding 8 μA is flowing while the animal is moving. From biological point of view this is ineffective. The natural movement of the animal will be disturbed only by an intensity exceeding 15 μA. The counter connected in series with the anode will be operated at a D.C. voltage of 320V which — in view of the anode values of the tube of 250 V 45 mA according to the catalogue — means an operation at an anode current of 32 mA. On counting, the animal closes grid-cathode poles during its movement. The supply voltage is rectified from a secondary mains transformer type 167, from 2 × 320V 120mA by means of full wave rectifier valve AZ4. The buffer condenser is of 16 μF. The negative bias voltage is produced by a tube 6 × 4 by means of voltage division taken from the cathode with the aid of a condenser 8 μF 50/100 V. For filtering any possible counting hum, a condenser of 3 n (nanofarad) is inserted between grid and cathode. Necessary counting speed is 360-350/minute.

For the construction of the instrument small 5-digit relays type BHG have been used; for this type shunt is necessary owing to a too strong

operation. Grid and cathode terminals are insulated on plates of appropriate size and by varying their polarity the required movements may be counted.

Small devices for pharmacological experiments.

Wiring diagram of the device is shown in Fig. 1. By leading the required supply voltages through the terminal located at the side of the instrument any number of additional channel units may be connected to the channel built-in in this design of the device. In this way a multi-

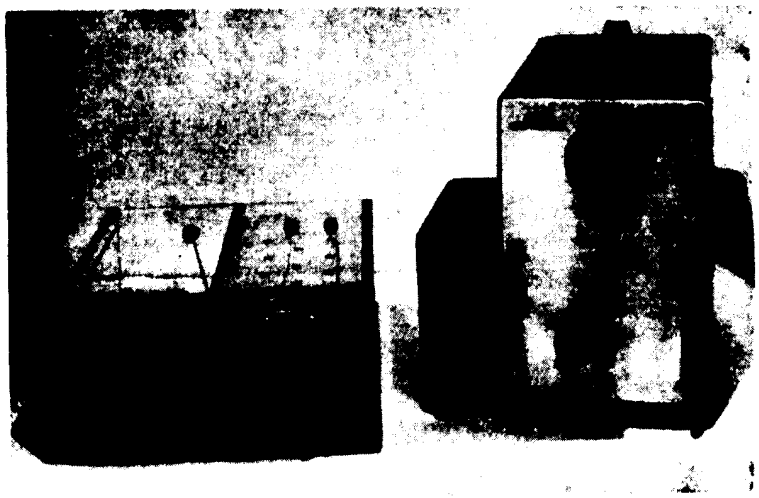


FIG. 2

channel device may be developed. Fig. 2 shows a small two-channel device for experiments on mice. On the front panel of the instrument are located: mains switch plus signal light, counter and instrument measuring supply voltage between anode and ground basic instrument 5 mA RFT/. A circuit breaker is applied for saving the instrument. The terminals for mains connection, voltage transformer and measuring body are located at the rear side. The measuring terminals of the second unit are likewise at the rear side. The box of the measuring unit is of plexy-glass, while the measuring body consists of nickel-plated copper sheets.

Large instruments for physiological and pharmacological experiments on mice and rats.

The instrument is a developed form of the principle shown in Fig. 1. Fig. 3 shows the front panel, Fig. 4 the instrument with the measuring

area belonging to it. In the Figure the measuring instrument is located on a small table and the measuring area on a bigger one. The latter contains ninety-six 12 × 9,5 cm aluminium sheets. Their wiring diagram

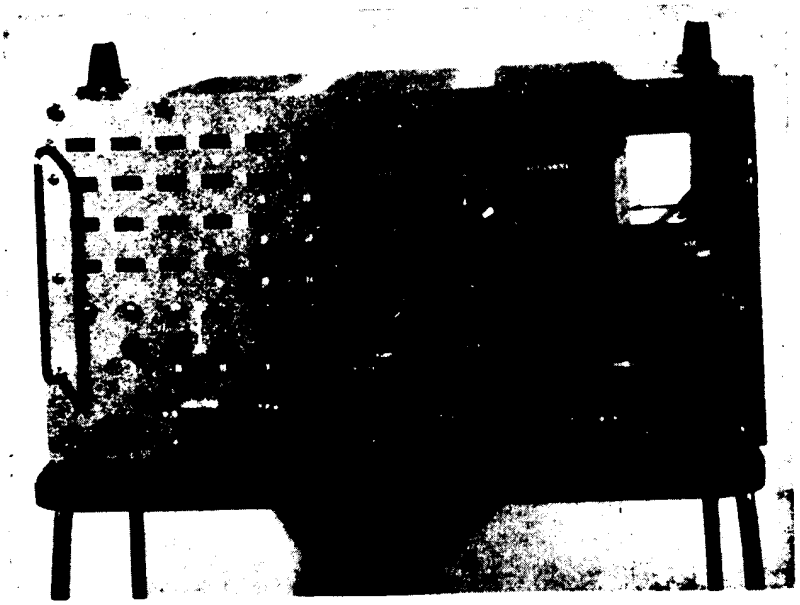


FIG. 3

is shown in Fig. 5. The measuring area is connected to the instrument by two 52-pole terminals, one of which is a 3-octal terminal + 1 ground

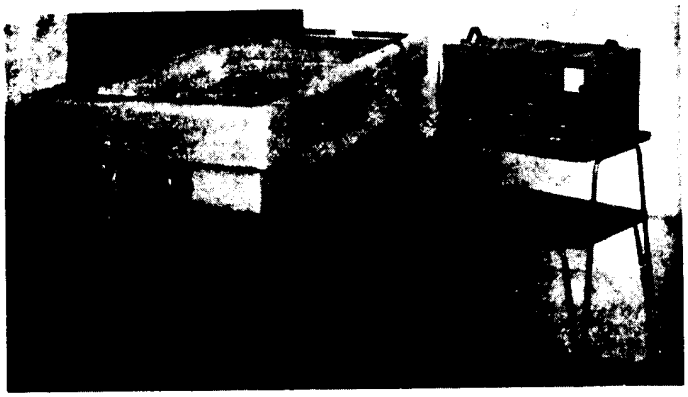


FIG. 4

point termination, the other is 1 octal head with 1 ground point. Sketch of the terminals is shown in Fig. 6.

With that system three kinds of measurements may be performed:

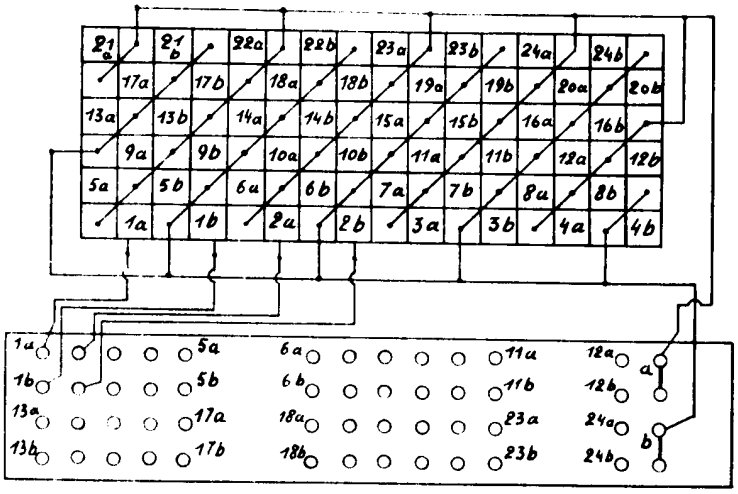
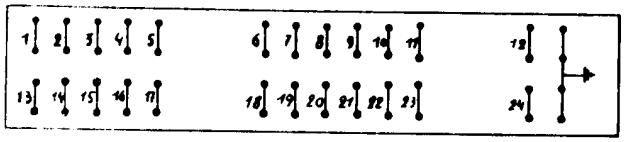


FIG. 5

Arrangement of measuring area

1) With the aid of the 24-channel terminal (see FIG. 6) on 24 × 4 sheets may be measured separately. One counter each belongs to four sheets (see FIG. 3). The 24 measuring channels are then separated by



„24 CHANNELS" CONNECTION

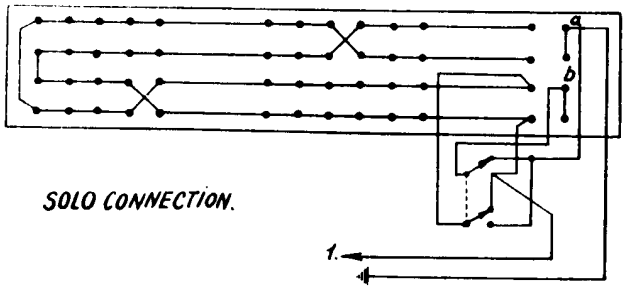


FIG. 6

plexy-glass plates from one another. In this manner the motility of 24 mice may be measured simultaneously separately.

2) The instrument may be changed over to a counter with the aid of the solo-terminal (see FIG. 6, see also solo counter in FIG. 3). With this method the movement of a mouse can be measured in the entire equipment.

3) In the other position of the solo switch the motility of a rat can be measured by the instrument (see FIG. 6). In such a case four neighbouring sheets form one sheet from the point of view of measurement in accordance with the body-size of the rat and the animal closes the circuit only if it passes through between such "large sheets". The measuring area consists in such cases of 24 large sheets altogether.

On the front panel of the instrument (see FIG. 3) 24 counters (6 - 4) and the following control organs are located:

1) Main switch (which switches the supply unit and at the same time produces the bias voltage).

2) Supply units II-VI (by switching one supply unit four channels each are put into operation).

3) Automatic channel change over switch (with sole or 1-24 positions; for measuring one animal — mouse or rat — sole position, for the measurement of several animals, position 1-24).

4) Automatic time switch.

5) Sole-counter.

6) Magic eye.

7) Measuring instrument to check the device (this may be used in two different positions: in "anode" position for measuring the supply voltage of the six supply stages and in "channel" position for measuring the 24 channel grid-cathode points).

8) 3 octal terminals for connection to the measuring body.

Directions for the use of the device:

After having connected mains to terminal on the rear side of the instrument, switch-on main switch. Thereby supply unit I has been put into operation which is indicated by the red light of the scale lamp. The switches of the supply units below the counter are switched-on if the movement on a small area of several mice has to be measured simultaneously. The device is in measuring condition if with the automatic channel change over button brought into "solo" position, the magic eye lights in bright green colour. Thereafter ascertain with the aid of the measuring instrument, whether the supply stages are in order and whether there is no shortcircuit in the channels. Shortcircuit is caused

by wet impurity between the clearences, therefore keep the measuring area carefully clean. In the case of shortcircuit, the meter indicates by deflection if a shortcircuited channel is being switched on. Having made sure that all 24 channels are in good working condition, connect measuring area and instrument by means of the appropriate terminal. During the measurement the top of the device is shut up by a thick plexy glass sheet moving on rails. Approximately 30 sec after switching-in, the tubes are heated up. The required measuring time is adjusted by the automatic time switch; when time is up the device is switched on automatically. Anode current is flowing only during the time of counting, this results in power consumption. If the counters are located in the cathode circuit, the position is just the opposite. Total consumption of the device is appr. 320 W.

The reading of the counters can be made fully automatic. As Fig. 7 shows there are in addition to the large instrument and the measuring

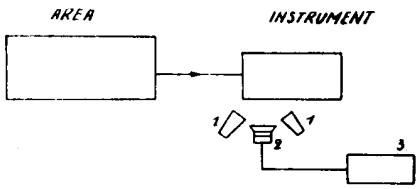


FIG. 7

1. Flash light
2. Robot (Tessar 28)
3. Relèe

Schematic arrangement for automatic measurements

body also a flash light and a camera stand in front of the instrument. The exposures are facilitated by placing a half-round plexy-glass row in front of the counters. In this way the numbers on the picture can be easily read. The camera is a reporter apparatus "ROBOT" (Tessar 2.8) which can take 14 pictures. A usual clock work serves for actuating the trigger at the required time, which is provided with a contact-giving disc on the spindle in stead of the hands. The mechanism is mounted on an insulating frame since it is live. The contact-knobs of the disc are rotating in front of the other point of the cutoff circuit. Intervals of contact are variable by placing an appropriate number of metal contacts into the disc, highest frequency being 5 minutes. The disc is of plexy-glass, behind which a metal plate is inserted. The disconnected circuit operates a magnetic relay at the time of switching which actuates the trigger by means of a lever transmission.

RESULTS

Quantitative assessment of drug-induced motility.

In the motility test a dose-response curve is plotted for each drug, in 6 to 8 doses. Every point in the curve represents the mean for at least 24 animals. In the first step of the test the motility of untreated animals

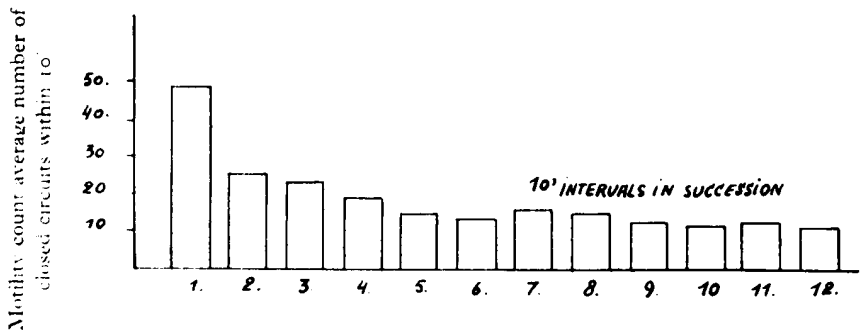


FIG. 8

Motility of control animals; average of measurements made on 480 animals.

is measured for a period of 1 hour. In the second step the psychostimulant is injected subcutaneously and the measurement is continued for 1 hour, taking readings at 10-minute intervals.

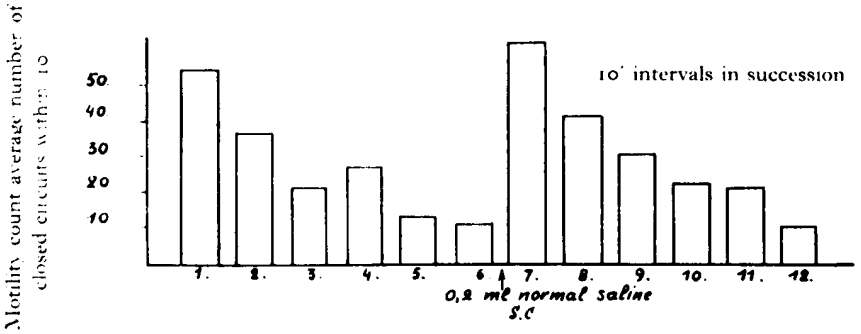


FIG. 9

Effect of normal saline injection on motility. (Average of measurements made on 96 animals).

The "normal" motility of the controls shows a very wide range of individual variation. The measurements made in 480 mice yield the result shown in Fig. 8. As it is visible, the motility value is the highest

during the first 10 minutes, then decreases sharply and, showing a steadily declining tendency for 2 hours, the average motility becomes set at a low level.

Fig. 9 shows the responses of 96 mice to the subcutaneous injection of 0.2 ml of physiologic saline solution. The injection was given after the one-hour control period and, as it may be seen, produced a definite increase of motility. The value at the 2nd hour reached the motility value for the first hour, but the change is too small to be relied upon in evaluating the hypermotility response to psychostimulants.

In Fig. 10 are presented the dose-response curves for four drugs producing hypermotility. Although the responses to single doses were invariably recorded after a control period, the mean for the 480 animals

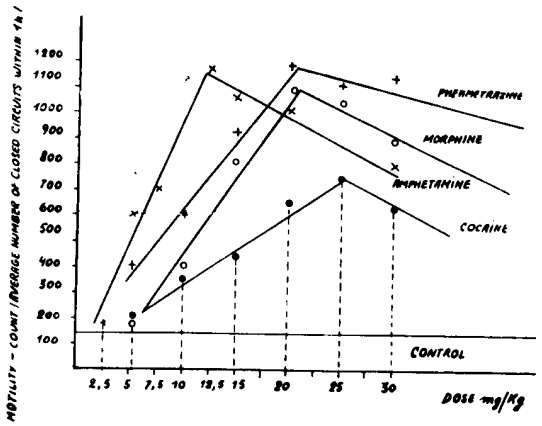


FIG. 10

Dose-response curves of psychostimulants. (Every point represents an average of 48 mice).

(140) is relied upon as the stable control and is denoted by a line parallel with the abscissa. In the figures the abscissa shows the dose, the ordinata the "motility count", which means the average number of short-circuits counted during the 1 hour period following injection. Each point in the dose-response curves presented in Fig. 10 stands for the mean of measurements made in 48 animals. The data indicate that within certain limits there was a linear correlation between the size of the dose and the measure of motility, as determined in the motimeter. Over a certain limit, however, the "motility count" decreases when the dose is further increased. Of the four compounds (amphetamine, phenmetrazine, morphine and cocaine) tested amphetamine proved to be the most potent.

The motimeter showed the effect of caffeine, and in some measure also that of high doses of nikethamide. As it is indicated by Fig. 11, caffeine was effective in relatively small doses, as compared with the dose of 500 mg/Kg that produces convulsions. In the dose range of from 25 to 150 mg/Kg a linear correlation between dose and response was observable, although the variations were considerable. In relatively

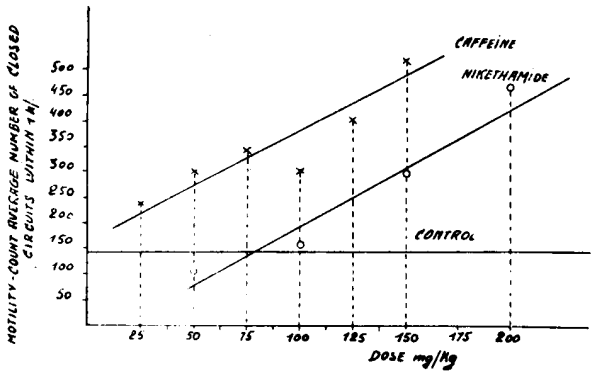


FIG. 11

Effect of caffeine and nikethamide. (Every point represents an average of 48 animals).

high doses (150 to 200 mg/Kg), nikethamide increased motility in a not too great, but significant measure, but the 300 mg/Kg dose produced convulsions. Even small doses of the drastic convulsants, such as e.g. strychnine and pentamethazol, fail to induce hypermotility. We used the drugs in non-convulsant doses. The results, presented in Table I, make it clear that these compounds greatly inhibited normal motility.

TABLE I

Effect of pentamethazol and strychnine on the normal motility of mice

Compound	Dose, mg/Kg	Number of animals	Motility-count
Control	--	480	140
penthamethazol	25	24	86
	50	24	17
strychnine	0.25	24	81
	0.5	24	42

Subconvulsant doses of pentamethazol antagonize the action of psychostimulants (TABLE II). Strychnine has no such effect.

TABLE II

Effect of pentamethazol on the psychostimulant-induced hypermotility
(Each dose has been tested in 24 mice and has been averaged)

Pentamethazol mg/Kg		Psychostimulant	Dose mg/kg	Motility-count
50		—	—	17
—		amphetamine	10	1147
50	+	amphetamine	10	530
—		phenmetrazine	20	1162
50	+	phenmetrazine	20	402
—		morphine	20	1089
50	+	morphine	20	186
—		cocaine	25	730
50	+	cocaine	25	580

The use of the motimeter in the quantitative measurement of the response to tranquilizers. As it is known, tranquilizers inhibit both the normal and the drug-enhanced motility. The so-called normal motility of the animal in the motimeter decreases with time (FIG. 8) and is very sensitive to depressant drugs. The hypermotility produced by psychostimulants is more resistent and often very great differences can be noted between the effects of tranquilizers on the hypermotility induced by various stimulants. For this reason, if a tranquilizer is tested against several psychostimulants at the same time, the results will be characteristic for the tranquilizer and may be relied upon in further investigations.

Less potent tranquilizers (minor tranquilizers) suppress only the very sensitive normal motility, while the more potent ones (major tranquilizers) inhibit also the drug-induced hypermotility. The major tranquilizers are so potent in this test that they inhibit the hypermotility induced even by supermaximal doses of psychostimulants. In Table III, are presented the results obtained for three major tranquilizers (reserpine, chlorpromazine and 6.7-dimethyl-2-methylpiperidinotetralon-1.HCl (N 702) (6) in tests against psychostimulants.

The data in Table III indicate that the tranquilizers tested were somewhat different in regard to their inhibitory actions. In a dose of 5 mg/Kg chlorpromazine suppresses the responses to all of the psychostimulants tested. The same dose of reserpine inhibits the response to morphine and cocaine, lessens the response to phenmetrazine, but is

TABLE III

Major tranquilizers tested against various drugs inducing hypermotility

Psychostimulants (dose 20 mg/Kg in every case		Tranquilizers (dose 5 mg/Kg in every case	Number of animals	Motility-count
amphetamine		—	48	1026
»	+	chlorpromazine	24	103
»	+	reserpine	24	990
»	+	N 702	24	330
phenmetrazine		—	48	1162
»	+	chlorpromazine	24	26
»	+	reserpine	24	419
»	+	N 702	24	496
morphine		—	48	1089
»	+	chlorpromazine	24	5
»	+	reserpine	24	2
»	+	N 702	24	194
cocaine		—	48	649
»	+	chlorpromazine	24	6
»	+	reserpine	24	7
»	+	N 702	24	249

inactive against the hypermotility induced by amphetamine. N 702 is qualitatively similar in action to chlorpromazine, but it is less potent.

The depressant action of a major tranquilizer can be best evaluated by examining in what way the dose-response curve for a psychostimulant is altered by a given dose of the tranquilizer. Supermaximal doses of psychostimulants (FIG. 10) are the best suited for use in such studies. Fig. 12 shows the effect of reserpine, chlorpromazine and N 702 on supermaximal doses of amphetamine. In these tests reserpine proved to be totally inactive, while chlorpromazine and N 702 were fully inhibitory in doses of 5 mg and 10 mg/Kg. Although chlorpromazine is more potent, the difference in its action on the amphetamine-induced hypermotility is hardly different from that of N 702.

The use of the motimeter in other kinds of experimental work. As the motimeter makes it possible to test numerous animals at the same time, dose-response curves composed of 6 to 8 points may be plotted in one day. Each point may stand for the average of the motility of 24 to 48 animals. This is a great advantage over previous methods, because

individual variations in motility are extreme and reliable quantitative evaluation requires measurements made in large numbers of animals. The motimeter is therefore a highly useful aid in routine pharmacological experiments as well. It may be employed also in studies of other problems. For example, the motimeter makes it possible to examine the so-called hunger motility of mice and rats. The importance of this type motility has been expounded in a previous paper (5) in regard to evaluation of the effect of tranquilizers. In such experiments the switches should be set as specified before.

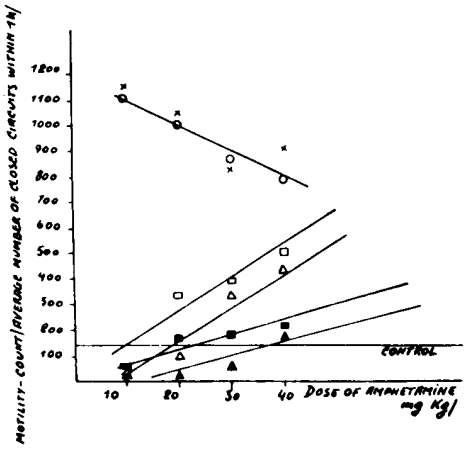


FIG. 12

Effect of major tranquillizers on hypermotility caused by amphetamine. (Every point represents an average of 24 mice).

o - - - - - o *amphetamine*
× - - - - - × *amphetamine*, 2h after injection of 5 mg/kg reserpine
□ - - - - - □ *amphetamine*, 30' after injection of 5 mg/kg N 702
△ - - - - - △ *amphetamine*, 30' after injection of 5 mg/kg chlorpromazine
■ - - - - - ■ *amphetamine*, 30' after injection of 10 mg/kg N 702
▲ - - - - - ▲ *amphetamine*, 30' after injection of 10 mg/kg chlorpromazine

The motimeter can also be used in more complex psychophysiological studies (object-search, the distance covered in search, the amount of motility required for finding the object, etc.). Problems of such nature have been dealt with in detail elsewhere (3, 4). On the basis of the principle on which the motimeter operates it is possible to measure quantitatively orienting and investigating motions, which play an important role in experiments concerned with active conditioned reflexes (3, 4). These problems will be discussed elsewhere.

SUMMARY

A sensitive electronic apparatus called the motimeter, suitable to measure the motility of small animals, is described. The motimeter proved to be a useful aid in psychopharmacological and psychophysiological work alike.

The motimeter operates on the following principle. The animal crosses over from one aluminium plate to an other 3 mm distant from it. This is recorded electronically and the frequency with which such a crossing occurs in a unit of time is determined.

The motimeter is suitable for use in studies on small animals, in which a quantitative measurement of "spontaneous" motility is required. Motility may be measured over short or long periods and in many animals (24 mice at a time). The measurement may be fully automatic.

The dose-response curve for a psychostimulant may be plotted within a few hours. The modification of these dose-response curves by tranquilizers may be likewise determined within a short time.

Using the motimeter, the dose-response curves have been plotted for the following drugs: amphetamine, phenmetrazine, morphine, cocaine and caffeine. The tranquilizers tested were: reserpine, chlorpromazine and 6,7-dimethyl-2-piperidinomethyltetralon-1.HCl (compound N 702).

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